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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/645,085	10/07/2002	Naoshi Fukushima	065678-0108	7376

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/645,085	FUKUSHIMA ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-17 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/7/05; 4/4/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner's Comments

1. It is noted that the Reply of December 16, 2005 stated that according to PAIR, the filing dates for the three Amendments filed for this application are January 1, 2004 (first preliminary amendment), August 23, 2004 (second preliminary amendment) and October 7, 2004 (third preliminary amendment). Applicants' comments regarding the three Preliminary Amendments are acknowledged. However, the actual filing dates of record for the three Preliminary Amendments of the instant application are January 24, 2003 for the first and second Preliminary Amendment and August 23, 2004 for the most recent Amendment.

The Examiner also acknowledges receipt of 43 sheets of replacement drawings in the Reply of December 16, 2005.

Priority

2. In reviewing the file history for the instant application,10/645,085, Applicants' co-pending application,10/257,864, and the Petitioner's Decision of August 25, 2003 regarding both applications, the Examiner acknowledges that the instant application under 35 USC 111(a) is a C-I-P of PCT/JP01/03288 with a U.S. filing date of October 17, 2002 and a PCT filing date of April 17, 2001. The 10/257,864 application, although having entered U.S. National Stage on October 17, 2002 from PCT/JP01/03288, will be processed as a national stage application under 35 U.S.C. 371, and has been accorded

a U.S. filing date of June 24, 2003 pursuant to Applicant's having filed a complete Oath/Declaration on said date.

In the Reply of December 16, 2005, Applicants requested that receipt of certified copies of the three priority documents be verified. The certified copies of the three foreign priority documents do not appear to have been filed with the National Stage application, 10/257,864, upon entry, and copies have not been provided for the instant application.

Election/Restrictions

3. Applicant's election without traverse of Group IV (claims 18, 19) in the reply filed on December 16, 2005 is acknowledged. It is noted that the Reply stated that this is a "provisional election" and this is interpreted as being "without traversal". In addition Applicant provided no response as to why the restriction was not proper.

Claims 18 and 19 are the pending claims under examination. Claims 1-17 and 20-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions of Groups I-III and V, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 16, 2005.

Information Disclosure Statement

4. The Examiner has considered the U.S. patent reference, the WO references, the foreign reference as well as the non-patent literature references cited in the IDSs submitted on April 4, 2003 and March 7, 2005. Accordingly, the references have been entered and made of record.

Specification

5. The specification is objected to for improper arrangement. As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order: a Brief Summary of the Invention followed by a Brief Description of the Drawings should be inserted at page 4 between the sections for the Background of the Invention and the Detailed Description of the Invention. Applicants' description of the figures is noted on pages 92-101 of the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point

a. Claim 18 is indefinite for reciting "purifying a dimer of the single chain Fv produced in the medium" as it is unclear whether the scFv is produced in the medium by

culturing host cells, or whether the dimer is produced in the medium once the scFV is expressed by host cells.

b. Claim 19 recites (in step b for purposes of examination) "and to form a dimer of the single chain Fv." The claim is directed to stabilizing "a dimer", so it is unclear whether the dimer of step b is the stabilized dimer, or whether it is an intermediate to the formation of a stabilized dimer.

7. Claims 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

a. The omitted steps of Claim 18 are: the steps describing how a $(scFv)_2$ dimer is produced from a secreted scFv before the dimer is purified.

b. The omitted steps of Claim 19 are: the steps describing 1) how a $(scFv)_2$ dimer is produced from a secreted scFv; and 2) how the $(scFv)_2$ dimer is stabilized upon being formed from a scFv. It is unclear which elements contributing to the stabilization of the dimer are contemplated. Does the serum-free medium, and/or do the scFv chains contain structural features, that create and stabilize the dimers?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing and stabilizing a scFv

dimer by non-covalent bonding while expressed in the serum-free cultured medium from an animal cell, does not reasonably provide enablement for methods of producing or stabilizing any dimer derived from just any host cell-expressed scFv in the presence of serum-free medium alone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Claims 18 and 19 are very broadly drawn to any single chain Fv being expressed by any animal cell and secreted into serum-free medium in order to produce a stable dimer thereof in the medium.

For this field of art, many attempts to generate multivalent forms of scFv molecules, scFv dimeric, and trimeric molecules have been studied. One method is to link the domains with a peptide to generate scFv. Single chain Fvs with a 15-residue linker have been shown to form both dimers and monomers (Kortt et al. (Eur. J. Biochem 221:151-157 (1994); Desplancq et al. (Protein Eng. 7:1027-1033 (1994); and Kortt et al. (Protein Eng. 10:423-433 (1997)). Another approach has been to engineer

cysteine residues into specific cites in conserved framework residues of Fv molecules, thus forming a disulphide bridge that holds them together (Reiter et al. (Biochemistry 33:5451-5459 (1994); Reiter et al. (Protein Eng. 7:697-704 (1994)).

The scope of reagents used to crosslink a scFv into a dimer and/or the structural modifications that are introduced into a scFv to produce a dimer are taught in the specification (p. 5, line 19 to p. 6, line 10; p. 15, line 12 to p. 17, line 14; p. 20, line 25 to p. 21, line 15; p. 22, line 23- to p. 23, line 5). More specifically, the specification teaches at p. 5, line 19 to p. 6, line 10:

> "...single chain Fv dimer includes a dimer by non-covalent bond, a dimer by covalent bond through a crosslinking radical and a dimer through a crosslinking agent (an antibody, an antibody fragment, or bivalent modified antibody)...",

and at p. 17, lines 15-24:

> "To form a dimer of the single chain Fv it is preferable to select a linker suitable to dimerize in the solution such as culture medium more than 20%, preferably more than 50%, more preferably more than 80%, most preferably more than 90% of the single chain Fv produced in host cells. Specifically preferable is a linker composed of 2 to 12 amino acids, preferably 3 to 10 amino acids or other linkers corresponding thereto."

The specification teaches specific embodiments of scFv dimers against human MABL-1 and MABL-2 expressed by CHO cells in serum-free medium by methods shown in Examples 5 and 6.

In example 5.1 to 5.9, the specification teaches that a scFv fragment of MABL with a flexible 15-residue linker was designed to have in successive order from the N terminus, the V_H region, a flexible linker $(Gly_4Ser)_3$, the V_L region, and an epitope tag, FLAG. Example 5.9(3) shows that a MABL-2 scFv monomers and dimers were purified

from CHO cell cultures and that "more than 90% of the dimer in the dimer fraction was stably preserved for more than a month at 4°C." (p. 50, lines 14-15). The results also demonstrate that the dimer was not linked by disulfide bonds but is a non-covalent dimer.

Other scFv MABL dimers, [sc(Fv)$_2$], were constructed in Example 6.1-6.9 having two H chain V regions and two L chain V regions and amino acid linkers of variable length (3-7 amino acids). These experiments show that the MABL2-scFv and -sc(Fv)$_2$ comprising the linker of SEQ ID NO: 44 (5 amino acids) yielded the greatest amount of dimer in CHO supernatants, with the dimer being stable for a month at 4°C after purification.

Thus Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed methods in a manner reasonably correlated with the scope of the claims broadly including just any number or kind of single chain Fv much less that the molecule can be expressed by cells in culture to further undergo dimerization. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19, 24 (CCPA 1970).

Without such guidance, the changes which can be made in the structure of the single chain Fv and still maintain dimerization properties under culture conditions is unpredictable and the experimentation left to those skilled in the art is unnecessary and improperly extensive and undue. See Amgen, Inc v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026, 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Therefore, the skilled artisan at the time the invention was made recognized the lack of predictability of the nature of the art and state of the prior art to which the instant invention pertains. Also, such disclosures clearly indicate that the amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made. In view of the undue experimentation that would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in Applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for producing and stabilizing a dimer of a scFv molecule expressed and secreted by animal cells into culture medium, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 18 and 19 are rejected under 35 USC 102(e) as being anticipated by Fukushima et al (U.S. 20040073013; filed March 12, 2001; published June 12, 2003; hereinafter referred to as "Fukushima").

Claim 18 recites a method for producing a dimer from a serum-free culture medium in which an animal cell is cultured to express a scFv from which the dimer is formed.

Claim 19 recites a method for stabilizing a dimer from a serum-free culture medium in which an animal cell is cultured to express and to secrete a scFv, and from which the dimer is formed.

Both claims 18 and 19 are anticipated by Fukushima because the reference teaches each and every element of the claims and the reference is by another.

Fukushima discloses a process for producing and stabilizing a dimer of the single-chain Fv which comprises culturing host mammalian cells producing the single-chain Fv in a serum-free medium to secrete the single-chain Fv into the medium and isolating the dimer of the single-chain Fv formed in the medium. ([0016]; Examples 5 and 6).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claim 18 is rejected under 35 U.S.C. §103(a) as being obvious over Kortt et al. (Protein Eng. 10:424-433 (1997); hereinafter referred to as "Kortt") in view of Dorai et al. (Biotechnology (NY) 12(9):890-897 (1994); hereinafter referred to as "Dorai") as evidenced by Verma et al. (J. Immunol. Methods 216:165-181 (1998); hereinafter referred to as "Verma") and further in view of Keen et al. (Cytotechnology 18:207-217 (1995); hereinafter referred to as "Keen").

Claim 18 recites a method for producing a dimer from a serum-free culture medium in which an animal cell is cultured to express a scFv from which the dimer is formed.

Kortt discloses the production of single-chain Fv constructed by joining the V_H and V_L domains with 10-residue $(Gly_4Ser)_2$ and five-residue (Gly_4Ser) linkers to produce a dimer thereof in E. coli. Kortt does not teach expressing the scFv molecule in an animal cell under serum-free conditions to be secreted into the medium.

Dorai discloses expression and secretion of scFv into culture medium of transfected cells, namely, 293 cells, CHO and Sp2/0 cell lines.

Keen teaches a cell culture system using animal cells grown in serum-free medium for growing monoclonal antibodies, and that the antibodies remained functionally active.

It would have been prima facia obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a dimer from an scFv expressed from an animal cell grown under serum-free conditions in view of Kortt, Dorai and Keen.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the instant claimed method of producing a dimer in view of Kortt, Dorai and Keen. Kortt disclosed structural linkers engineered into the scFv to enhance dimerization. In the case of antibody fragments, a wide range of sFV and scFv-fusion proteins were already known to have been expressed in mammalian cells (Verma, p. 176, Col. 1, ¶2- Col. 2, ¶1). Dorai is discussed in Verma's review article as demonstrating mammalian cell line expression of scFv molecules amongst the work of others. Dorai showed scFv secretion for animal cells lines. Keen exploits a serum-free cell culture system for growing monoclonal antibodies and which enhances the yield of the antibodies produced. The glutamine synthetase gene NOS system used in Keen can also be used to produce high levels of a chimeric antibody (Verma, p. 176, Col. 1, ¶1).

Thus it would also have been obvious to modify Kortt's scFv to obtain a dimer produced under culture conditions of Keen using a mammalian cell of Dorai for purification of the dimer.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

11. Claim is 18 rejected under 35 U.S.C. §103(a) as being obvious over Fukushima et al. (WO 00/53634; filed March 10, 2000; published September 14, 2000; hereinafter referred to as "Fukushima"; English language equivalent obtained from EPO website (esp.cenet) attached to WO reference) in view of Kortt et al. (Protein Eng. 10:424-433 (1997); hereinafter referred to as "Kortt") and further in view of Keen et al. (Cytotechnology 18:207-217 (1995); hereinafter referred to as "Keen") as evidenced by Verma et al. (J. Immunol. Methods 216:165-181 (1998); hereinafter referred to as "Verma").

Claim 18 recites a method for producing a dimer from a serum-free culture medium in which an animal cell is cultured to express a scFv from which the dimer is formed.

Fukushima discloses a process for producing scFVs which comprises culturing in animal host cells and extracting the secreted scFvs from the culture thereof ([0022]; Example 5.4). Fukushima does not disclose that the secreted scFvs undergo dimerization in the culture medium or culturing animal host cells in serum-free medium.

Kortt discloses the production of single-chain Fv constructed by joining the V_H and V_L domains with 10-residue $(Gly_4Ser)_2$ and five-residue (Gly_4Ser) linkers to produce a dimer thereof in E. coli.

Keen teaches a cell culture system using animal cells grown in serum-free medium for growing monoclonal antibodies, and that the antibodies remained functionally active.

It would have been prima facia obvious to one of ordinary skill in the art at the

time the claimed invention was made to have produced a dimer from an scFv expressed from an animal cell grown under serum-free conditions in view of Fukushima, Kortt and Keen.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the instant claimed method of producing a dimer in view of Fukushima, Kortt and Keen. Kortt disclosed structural linkers engineered into the scFv to enhance dimerization. Fukushima discloses expression and secretion of scFv by CHO cells in culture medium. In the case of antibody fragments, a wide range of sFV and scFv-fusion proteins were already known to have been expressed in mammalian cells (Verma, p. 176, Col. 1, ¶2- Col. 2, ¶1). Kortt disclosed structural linkers engineered into the scFv to enhance dimerization and to improve targeting over the monovalent species like scFv and Fab. Keen exploits a serum-free cell culture system for growing monoclonal antibodies and which enhances the yield of the antibodies produced. The glutamine synthetase gene NOS system used in Keen can also be used to produce high levels of a chimeric antibody (Verma, p. 176, Col. 1, ¶1).

Thus it would also have been obvious to modify Fukushima's scFv to obtain a dimer of Kortt and produced under culture conditions of Keen using a mammalian cell of Fukushima for purification of the dimer.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

12. Claim 19 is rejected under 35 U.S.C. §103(a) as being obvious over Reiter et al. (Biochemistry 33:5451-5459 (1994))); hereinafter referred to as "Reiter") in view of Dorai et al. (Biotechnology (NY) 12(9):890-897 (1994); hereinafter referred to as "Dorai") as evidenced by Verma et al. (J. Immunol. Methods 216:165-181 (1998); hereinafter referred to as "Verma") and further in view of Keen et al. (Cytotechnology 18:207-217 (1995); hereinafter referred to as "Keen").

Claim 19 recites a method for stabilizing a dimer from a serum-free culture medium in which an animal cell is cultured to express and to secrete a scFv, and from which the dimer is formed.

Reiter discloses the production of a stable single-chain Fv constructed by joining the V_H and V_L domains with cysteine residues to produce a disulphide dimer thereof in E. coli. Kortt does not teach expressing the scFv molecule in an animal cell under serum-free conditions to be secreted into the medium.

See the Examiner's comments with respect to Dorai and Keen under section 10, *supra*, as they apply here.

It would have been prima facia obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a dimer from an scFv expressed from an animal cell grown under serum-free conditions in view of Reiter, Dorai and Keen.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the instant claimed method of producing a dimer in view of Reiter, Dorai and Keen. Reiter disclosed cysteine residues

engineered into the scFv to stabilize dimerization. Reiter also discloses that disulphide scFvs are more stable than scFv's containing a peptide linker (p. 5458, Col. 2, ¶3). In the case of antibody fragments, a wide range of sFV and scFv-fusion proteins were already known to have been expressed in mammalian cells (Verma, p. 176, Col. 1, ¶2-Col. 2, ¶1). Dorai is discussed in Verma's review article as demonstrating mammalian cell line expression of scFv molecules amongst the work of others. Dorai showed scFv secretion for animal cell lines. Keen exploits a serum-free cell culture system for growing monoclonal antibodies and which enhances the yield of the antibodies produced. The glutamine synthetase gene NOS system used in Keen can also be used to produce high levels of a chimeric antibody (Verma, p. 176, Col. 1, ¶1).

Thus it would also have been obvious to modify Reiter's scFv to obtain a stabilized dimer produced under culture conditions according to Keen using a mammalian cell according to Dorai.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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